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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,045	10/21/2003	De-Chao Yu	CELL-018CON	8701

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,045	YU ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-88* is/are pending in the application.

4a) Of the above claim(s) *88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/21/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment and Declaration filed 6/6/06. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/6/06 has been entered.

Claims 1-58 have been canceled. Claim 74 has been amended. Claims 59-88 are pending in this application. Claim 88 has been withdrawn from examination. Therefore, claims 59-87 are under examination in this application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 59- 62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 are rejected under 35 U.S.C. 102(a) as being anticipated by Chang et al (WO 99/25860; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and 12/22/05 and restated below.**

Chang et al teach an adenovirus vector that is selectively replicative and comprises gene for replication under control of a tissue specific promoter that further comprises transgenes. The transgene and the gene essential for replication can be linked by an IRES (see e.g. page 18, paragraph 2, page 29, paragraph 2 and figure 7). The gene essential for replication is any adenoviral gene that is essential for replication such as early or late genes (see e.g. page 15, paragraph 5). Specifically cited are E1A, E1B, E2, E3 or E4 (see e.g. bridging paragraph page 21-22). However, the specification teaches that the gene is essentially any gene that is required for the life cycle of the virus, which inherently includes late genes (see e.g. page 32, paragraph 2). Tissue specific promoters contemplated for use are mucin, CEA, PSA, tyrosinase or AFP (see e.g. page 29, paragraph 4). Cytotoxic genes include diphtheria toxin A, HSV-tk. Alternatively the transgene can be a cytokine such as GM-CSF or a reporter gene (see e.g. figure 1B, bridging paragraph 30-31 and page 29, paragraph 5). The first gene has a mutation in the transcriptional regulatory region, which comprises promoters and enhancers (see e.g. bridging paragraph page 17-18 and page 18, paragraph 2). It is inherent in the design of the construct that the second promoter be deleted of its endogenous promoter as the use of the IRES is for expression of the two genes by a singe regulatory sequence (see e.g. page 18, paragraph 2). This deletion constitutes a mutation in the promoter as recited in the claims. Cells and composition comprising the adenovirus are taught (see e.g. example 3). On page 16, Chang et al teach that the native transcriptional regulatory sequences may be rendered dysfunctional or may be disabled by partial removal (deletion) or other mutation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59- 62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Nanbru et al (JBC, 1997, Vol 272, pages 32061-32066). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and 12/22/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element. The second gene has a mutation or a partial deletion of its endogenous promoter and is under translational control of an internal ribosome entry site (IRES). Furthermore

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach that the second gene has a partial deletion in its promoter.

Nanbru et al teach construction of a bicistronic vector for expression of a first and second coding sequence separated by a c-myc leader sequence (see e.g. figure 1). The leader sequence comprises the native promoters as well as leader sequences (see e.g. page 32061, col 1, paragraph 3). The native c-myc promoters are partially deleted in the bicistronic vector (see e.g. figure 1) to delete promoter P0, P1 and then P2. The goal is to initiate transcription from some

or all of these promoters but to allow for cap-independent initiation of translation of the second gene within the bicistronic vector.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a partial deletion in the promoter of the 2nd gene as taught by Nanbru et al in the bicistronic vector as taught by Chang et al because Chang et al teach that it is within the ordinary skill of the art to generate a bicistronic vector with a 1st and 2nd gene separated by an IRES and because Nanbru et al teach that it is within the ordinary skill of the art to delete the promoter of the 2nd gene. One would have been motivated to do so in order to initiate transcription from some or all of these promoters but to allow for cap-independent initiation of translation of the second gene within the bicistronic vector. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 63, 64, 66 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) as applied to claim 59-62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 above, and further in view of Yu et al (Cancer Research, 1999; see entire document) or Lin et al (PNAS, 1995; see entire document) or Roelvink et al (US 2001/0047081; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and 12/22/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of a TRE that is from human glandular kallikrein or uroplakin or E2F-1. Chang et al do not teach that the transgene is a reporter such as luciferase or β-glactosidase.

Yu et al teach identification of the transcriptional regulatory sequence of human kallikrein 2 (hK2) that is selectively inducible in prostrate to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Yu et al generated a recombinant adenovirus comprising the hK2 promoter driving expression of luciferase to assay its activity and inducibility (see e.g. figure 1). Furthermore, to generate a selective replicating adenovirus, hK2 was used to express E1b in a vector also comprising E1A (see e.g. fig 4).

Lin et al teach identification of a promoter that is selectively expressive in the suprabasal urothelial cells (see e.g. abstract). The urothelial promoter sequences are linked to a reporter gene, β -galactosidase and its tissue specificity was assayed. The promoter was expressive only in bladder (see e.g. figure 4 and 5).

Roelvink et al teach that the E2F promoter provides targeted gene expression in prostate cancer cells (see e.g. paragraph 0023).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tissue specific promoter taught by Chang et al with the kallikrein

promoter or uroplakin II promoter or E2F promoter taught by Yu et al or Lin et al or Roelvink et al because Chang et al teach that it is within the ordinary skill of the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al and Lin et al and Roelvink et al teach that it is within the ordinary skill of the art to use kallikrien, E2F and uroplakin promoters for tissue specific expression. One would have been motivated to do so in order to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 71 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) as applied to claim 59-62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 above, and further in view of Perez and White (Journal of Cell Biology, 1998; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and 12/22/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of Fas as the cytotoxic gene in which E1B 19K is deleted.

Perez and White teach that Fas mediated apoptosis leads to cell killing triggered by Fas ligand. E1B 19K blocks Fas mediated apoptosis (see e.g. abstract). It would have been obvious to delete E1B 19K in an adenovirus carrying FAS for the cytotoxic effects of Fas mediated apoptosis to occur.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cytotoxic transgene expressed by the adenovirus taught by Chang et al with a FAS gene in which the E1B 19K gene is deleted or mutated based upon the teachings of Perez and White because Chang et al teach that it is within the ordinary skill of the art to express a cytotoxic gene from adenovirus for cell killing and because Perez and White teach that Fas cell killing is blocked by E1B 19K. One would have been motivated to do so in order to receive the expected benefit of unhampered apoptotic cell killing in conditions taught by Chang et al in which cell killing is desired. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) as applied to claim 59-62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 above, and further in view of Stein et al (Molecular and Cellular Biology, 1998; see entire document) or Borman et al (NAR, 1995; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and 12/22/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of specific IRES sequence such as from EMCV or VEGF.

Stein et al teach isolation and utilization of the VEGF IRES that is effective in promoting cap-independent translation of mRNA (see e.g. abstract). Stein et al teach that the advantage of the VEGF IRES is the capacity for cap-independent translation in situations when overall protein synthesis is compromised (see e.g. page 3115, col 2). Internal ribosome entry is said to improve the competition with other mRNAs which otherwise would have rendered the translation of the mRNA an inefficient process (see e.g. page 3118, col 1).

Borman et al compare the activity of a variety of IRES sequences. EMCV is the most efficient at mediating expression (see e.g. figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IRES taught by Chang et al with the VEGF IRES sequence such as described by Stein et al or the EMCV IRES as described by Borman et al because Chang et al teach that it is within the ordinary skill of the art to express a bicistronic and because Stein et al and Borman et al teach that it is within the ordinary skill of the art to use IRES for bicistronic expression. One would have been motivated to do so in order to receive the expected benefit of cap-independent translation in situations when overall protein synthesis is compromised or for highly efficient expression. Based upon the teachings of the cited references, the high skill of

one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 10-14 of the amendment filed 6/15/05. Applicants argue that Chang et al do not anticipate the instant claims as they do not recite each and every element of the claims. However, applicants do not provide arguments as to the differences between the prior art and the instant invention. . Furthermore, applicants argue that the secondary references do not cure the deficiency of Chang et al.

Applicants' arguments filed 6/6/06 have been fully considered but they are not persuasive. Absent evidence to the contrary, the prior art anticipates Chang et al for the reasons set forth above. The Declaration filed on 6/6/06 under 37 CFR 1.131 but is ineffective to overcome the Chang et al reference. Consequently, it has been determined that it is not a proper Declaration under 37 CFR 1.131 and has been considered no further. Specifically, the Declaration has not been signed by all the inventors or alternatively accompanied by an affidavit or declaration by less than all named inventors of an application where it is shown that less than all named inventors of an application invented the subject matter of the claim or claims under rejection.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v.*

Eagle Mfg. Co., 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 59-62, 65, 75-79, 84 and 86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 15-21 of US application 10/947812, claims 9 and 15-21 of US application 10/624670 and 1-13 and 15-19 of US Patent No. 7,048,920. **These are new rejections.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 8 and 15-21 of US application 10/947812, claims 9 and 15-21 of US application 10/624670 and 1-13 and 15-19 of US Patent No. 7,048,920. That is, the cited claims of U.S. applications 10/947812 or 10/624670 or U.S. Patent No. 7,048,920 anticipate and fall entirely within the scope of the rejected claims of the instant application.

Specifically, each of the sets of claims recite a replication competent adenoviral vector comprising first and second genes separated by an IRES in which the genes are under transcriptional control of a transcriptional regulatory element (TRE) and the second gene has a deletion in its promoter.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding a patent from U.S. applications 10/947812 or 10/624670 or U.S. Patent No. 7,048,920, then two different assignees would hold a patent to the claimed invention of U.S. Patent 6,692,736, and thus improperly there would be possible harassment by multiple assignees.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER